PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/705 — A1

(11) International Publication Number: **WO 97/48401**

(43) International Publication Date: 24 December 1997 (24.12.97)

(21) International Application Number: PCT/US97/10453

(22) International Filing Date: 13 June 1997 (13.06.97)

(30) Priority Data:
60/019,978 17 June 1996 (17.06.96) US

(71) Applicant *(for all designated States except US)*: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HALPRYN, Bruce, Martin [US/US]; 3772 Ault Park Avenue, Cincinnati, OH 45208-1704 (US). LYON, Robert, Arthur [US/US]; 5940 Shallowcreek Drive, Milford, OH 45150 (US). CHANG, Yi-Chi [US/US]; Gibbon Road, Norwich, NY 13815 (US).

(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).

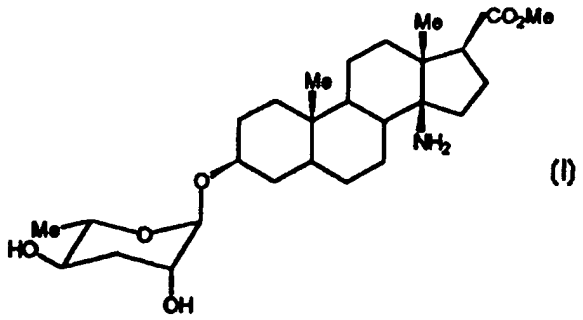
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DEOXY AND OXYGEN-SUBSTITUTED SUGAR-CONTAINING 14-AMINOSTEROID COMPOUNDS FOR USE AS AN ANTIARRHYTHMIC

(57) Abstract

A method of treating supraventricular arrhythmia and/or atrial fibrillation using a safe and effective amount of deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds and the pharmaceutically acceptable acid, salts or esters thereof of formula (I).



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

DEOXY AND OXYGEN-SUBSTITUTED SUGAR-CONTAINING 14-AMINOSTEROID COMPOUNDS FOR USE AS AN ANTIARRHYTHMIC

BACKGROUND OF THE INVENTION

This invention relates to deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds for use as antiarrhythmics. This invention also relates to pharmaceutical compositions containing these compounds.

In a healthy, structurally sound heart, the precise sequential electrical activation, then deactivation, of the entire cardiac muscle that occurs unerringly with each beat is characterized as normal cardiac rhythm. Arrhythmias are characterized as occurrences of abnormal electrical activity that can interfere with normal cardiac rhythm. The abnormal electrical activity can interfere with the initiation of, and/or the uniform spread of, the electrical wave (i.e. depolarization followed by repolarization of the cardiac muscle) that triggers the heart to contract.

Arrhythmias are generally classified into two types: 1) Supraventricular Arrhythmias (for example, atria fibrillation and flutter) and 2) Ventricular Arrhythmias (for example, ventricular tachyarrhythmia and ventricular fibrillation).

Supraventricular arrhythmias are generally not life-threatening. Individuals with these arrhythmias may experience a wide range of symptoms, from slight to severe intensity. These individuals may feel the physical sensation of missed beats, extra beats, and/or flutter, may occasionally feel slightly light headed or dizzy, and may have shortness of breath and/or chest pain. Since this situation is generally not life threatening, more aggressive therapies such as conventional antiarrhythmic drugs are usually not prescribed, because the side effects usually associated with them may not be acceptable for a non-life threatening condition.

Although supraventricular arrhythmia is not immediately life threatening, those suffering from atrial tachyarrhythmias may have an increased risk of stroke due to travleing thrombi induced by the tachyarrhythmia. Further those suffereing from chronic supraventricular arrhythmia may develop chronic heart failure (CHF). Congestive Heart Failure (CHF) is a progressive disease wherein the heart is increasingly unable to supply adequate cardiac output (CO), which is the volume of blood pumped by the heart over time, to deliver the oxygenated blood to the peripheral tissues. When the heart initially fails, the rest of the body compensates for the loss in CO and such compensatory mechanisms eventually result in the syndrome known as

CHF. As CHF progresses, structural and hemodynamic damages occur. Such structural damage manifests itself macroscopically as ventricular hypertrophy in the myocardium, and microscopically as interstitial, perivascular and replacement fibrosis in the ventricle wall, decreased myocardial capillary density, and myocardial cell death. When fibrosis of the myocardial tissue occurs it compromises the functioning of the heart because the remaining viable myocardial cells have a greater workload.

Digitalis and other cardiac glycosides are known for their cardiac inotropic effects (i.e. increasing cardiac contractility). It is also known that cardiac glycosides exert effects on the electrophysiological properties of the heart. The electrophysiological actions are exerted either indirectly through the autonomic nervous system (Rosen MR.; Weingart R) or directly through effect of the drugs on cardiac cell membrane properties (Weingart R; Hoffman). Cardiac glycosides act by blocking the transmission of the tachyarrhythmias from the atria to the ventricles. The arrhythmias remain in the atria. It has been discovered that the 14-aminosteroid compounds of the present invention terminate the arrhythmia in the artria allowing the entire heart to return to normal sinus rhythm. Thus, the 14-aminosteroid compounds of the prenset invention exhibit enhanced antiarrhythmic potential over other cardiac glycosides.

Cardioactive steroid nucleus-containing compounds have been described in the following patents: World Patent Publication WO 87/04167 to Chiodini, et al. published July 16, 1987 describes aminoglycoside steroid derivatives substituted by an amino-sugar residue at the 3-position and an acetal linkage at the 14-position. The disclosure states that the compounds are useful for the treatment of hypertension. French Patent 2,642,973 of Guina published August 17, 1990 describes a digitalis-like compound, 2,3-dioxymethyl-6-methyl-3-beta-D-glucose-strophanthidine, which contains the steroid nucleus substituted at the 3-position with a glucose moiety and at the 17-position with the lactone moiety, and at the 14-position with a hydroxyl group. The disclosure states that the compound is useful in preventing pathologic states resulting from cardiac insufficiencies for which digitalis is prescribed and for preventing pathologic states resulting from hypertension due to arterial calcification. The Guina compound is also alleged to be a positive inotrope, a peripheral vasodilator, and an antiarrhythmic agent. World Patent Publication WO 87/04168 to Chiodini et al., July 16, 1987 discloses an aminoglycoside steroid having an alkyl substituted amino sugar at the 3-position, such as 2-amino or 2-alkylamino-2-deoxy-hexopyranosyl, 3-amino or 3-alkylamino-3-deoxy-hexo-pyranosyl, 3-amino or 3-alkyl-amino-3,6-dideoxy-hexopyranosyl, 3 amino or 3-alkylamino-2,3,6-trideoxy-hexopyranosy 4-amino or 4-alkylamino 2,4,6-trideoxy-hexopyranosyl residues, and a

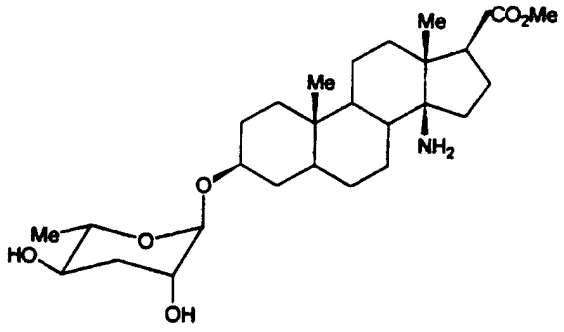
cyclic amide (lactam) at the 17-position. The 14-position is substituted with a hydrogen. The compound is said to be useful as an antihypertensive. World Patent Publication WO 91/17176 to Kenny, et al. published November 14, 1991, discloses a steroid glycoside, useful as a pressor agent, having a sugar moiety at the 3-position, such as a pentose, hexose or combinations thereof, and a lactone ring at the 17-position, the 14-position is substituted with an OH, H or a F, Cl, Br or NH2; and DD 296502 A5 to Siemann, et al. granted December 5, 1991 discloses a steroid amide for treating cardial insufficiency wherein the 3-position is substituted with a sulphonyl amino group and the 17-position is substituted with a 5 or 6-membered lactone ring; the 14-position is substituted with a hydroxy group. U.S. 5,144,017 to LaBella, September 1, 1992 discloses steroid compounds said to be useful as cardiac stimulants wherein the 3-position is substituted with a glycoside radical such as ß-D-glucoside, α-L-rhamnoside, tridigitoxoside and the 17-position is substituted with an acetoxy group or an amino group; and the 14-position has a hydroxy group; and U.S. 5,175,281 to McCall, December 29, 1992 discloses pyrimidinylpiperazinyl steroid compounds useful in treating spinal trauma, head injury and the subsequent cerebral vasospasm, preventing damage following cardiopulmonary resuscitation and cardiac infarction wherein the 3-position is hydroxy, CH_3O, COOH, or benzoxy, the 14-position is a hydrogen and the 17-position is a heterocyclic amine. DD 256,134 A1 to Wunderwald, et al., granted April 27, 1988 discloses a process for making cardioactive steroids wherein the 3-position of the steroid molecule is substituted with a morpholinoformyloxy residue, and the 17-position of the steroid molecule is substituted with a lactone ring; and the 14-position is substituted with hydroxy, hydrogen or an olefin. Said compounds are alleged to be useful for increasing cardiac contractility. JP 4-290899 to Ichikawa, et al., laid open October 15, 1992, discloses a cardiotonic steroid compound wherein the 3-position of the steroid nucleus is substituted with an oligosaccharide; wherein further said oligosaccharide consists of three glucopyranosyl moieties and the 14-position is substituted with an OH group, and the 17-position is substituted with a lactone ring. Templeton, et al., 36 J. Med. Chem. 42-45 (1993) disclose the synthesis of derivatives of 14-hydroxy-21-nor-5ß, 14ß-pregnane and 5ß, 14ß-pregnane C-3 α-L-rhamnosides and tris-ß-D-digitoxosides. Said compounds are reported to be effective cardiotonics. These derivatives, possessing a C-17ß $COCH_2OH$, CH_2OH, CO_2H, CO_2Me, CH_2NH_2, or CH_2NO_2 group, bind to the digitalis receptor recognition site of heart muscle. Templeton, et al.,1 J. Chem. Sci. Perkin. Trans., 2503-2517 (1992) disclose the synthesis of 20α- and 20ß-acetamido-, amino-, nitro- and hydroxy-3ß-glycoside (α-L-rhamnopyranoside and tris-ß-D-digitoxoside) and genin derivatives of 14-hydroxy-5ß, 14ß-pregnane together

with the C-20 oxime, hydrazone and amidinohydrazone. These compounds are asserted to be effective cardiotonics. Adeoti, S. B., et al., 12 Tetrahedron Letters, 3717-3730 (1989) disclose a method for introducing a 14ß-amino function into a steroid molecule. Said method allows for the preparation of the cardioactive 14ß-amino-5ß-pregnane-3ß, 20b diol.

The 14-aminosteroid compounds have been shown to be useful in treating CHF by increasing cardiac contractility. These compounds provide the therapeutic benefit of increased cardiac contractility without the side effects of digitalis. These 14-aminosteroids are described in the following three patents, all incorporated by reference herein: U.S. Patent 4,552,868, Jarreau, et al., issued November 12, 1985; U.S. Patent 4,584,289, Jarreau, et al., issued April 22, 1986 and U.S. Patent 4,885,280, Jarreau, et al., issued December 5, 1989. These three patents describe 14-aminosteroid compounds as possessing positive inotropic activity. The '868 patent also discloses 14-aminosteroid compounds having supraventricular anti-arrhythmic properties. PCT Application WO 95/08558, Liu et al., Pulbished March 30, 1995 describe the 14-aminosteroid compounds of the present invention, as more effective inotropes. The present invention relates to the surprising benefits of these compounds in the treatment of supraventricular arrhythmias and/or atrial fibrillation.

SUMMARY OF THE INVENTION

A method of treatment of humans or other mammals afflicted with supraventricular arrhythmias and/or atrial fibrillation comprised of administering to said human or other mammal a safe and effective amount of a deoxy and oxygen-substituted sugar containing 14-aminosteroid compounds and the pharmaceutically-acceptable acid salts or esters thereof of the formula:



DEFINITIONS AND USAGE OF TERMS

The following is a list of definitions for terms used herein.

"Aminosteroid" is a steroid ring compound having an amino group on the steroid nucleus.

"Alkyl" is an unsubstituted or substituted, straight-chain, cyclic or branched, saturated hydrocarbon chain having 1 to 8 carbon atoms, and preferably, unless otherwise stated, from 1 to 4 carbon atoms. Preferred alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, and butyl; a monovalent radical derived from an aliphatic hydrocarbon by removal of 1 H; as methyl. A lower alkyl group contains 1-6 carbon atoms.

"Heteroalkyl" as used herein is an unsubstituted or substituted, saturated chain having from 3 to 8-members and comprising carbon atoms and one or two heteroatoms.

"Alkenyl" is an unsubstituted or substituted, straight-chain or branched, hydrocarbon chain having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least one olefinic double bond.

"Alkynyl" is an unsubstituted or substituted, straight-chain or branched, hydrocarbon chain having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least one triple bond.

"Acetate": A salt of acetic acid containing the CH_3COO- radical.

"Acetoxy": Acetyloxy. The radical CH_3COO-.

"Acetyl": The acyl radical CH_3CO-.

"Aglycone": That component of a glycoside, e.g., plant pigment, which is not a sugar.

"Carbocyclic ring" or "Carbocycle" as used herein is an unsubstituted or substituted, saturated, unsaturated or aromatic, hydrocarbon ring, generally containing from 3 to 8 atoms, preferably 5 to 7 atoms.

"Heterocyclic ring" or "Heterocycle" as used herein is an unsubstituted or substituted, saturated or unsaturated or aromatic ring comprised of carbon atoms and one or more heteroatoms in the ring. Heterocyclic rings generally contain from 3 to 8, preferably 5 to 7, atoms. Unless otherwise stated, the heteroatom may be independently chosen from nitrogen, sulfur, and oxygen.

"Aryl" is an aromatic carbocyclic ring. Aryl groups include, but are not limited to, phenyl, tolyl, xylyl, cumenyl, and naphthyl; an organic radical derived from an aromatic hydrocarbon by the removal of one atom; e.g. phenyl from benzene. "Heteroaryl" is an aromatic heterocyclic ring. Preferred heteroaryl groups include, but are not limited to, thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, oxazolyl, thiazolyl, quinolinyl, pyrimidinyl, and tetrazolyl.

"Alkoxy" is an oxygen atom having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (e.g. -O-alkyl or -O-alkenyl); an alkyl radical

attached to the remainder of the molecule by oxygen; as, methoxy. Preferred alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, and alkyloxy.

"Hydroxylalkyl" is a substituted hydrocarbon chain which has a hydroxy substituent (e.g., -OH), and may have other substituents. Preferred hydroxyalkyl groups include, but are not limited to, hydroxyethyl, hydroxypropyl, phenylhydroxyalkyl.

"Carboxyalkyl" is a substituted hydrocarbon chain which has a carboxy substituent (e.g. -COOH) and may have other substituents. Preferred carboxyalkyl groups include carboxymethyl, carboxyethyl, and their acids and esters.

"Oxosilane" is an oxygen and silicone repeating unit Si-O-Si-O-, also known in the art as "siloxane."

"Aminoalkyl" is a hydrocarbon chain, (e.g. alkyl) substituted with an amine moiety (e.g. NH-alkyl-), such as dimethylamino alkyl.

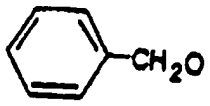
"Alkylamino" is an amino moiety having one or two alkyl substituents (e.g. -N-alkyl).

"Alkenylamino" is an amino moiety having one or two alkenyl substituents (e.g. -N-alkenyl).

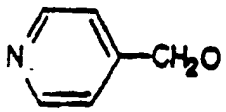
"Alkynylamino" is an amino moiety having one or two alkynyl substituents (e.g. -N-alkynyl).

"Alkylimino" is an imino moiety having one or two alkyl substituents (e.g., N=alkyl-).

"Arylalkyloxy" is an oxygen atom having an aryl alkyl substituent, e.g., phenylmethoxy or phenylmethyleneoxy



"Heteroarylalkyloxy" is an oxygen atom having a "heteroarylalkyl" substituent, e.g.,



"Arylalkyl" is an alkyl moiety substituted with an aryl group. Preferred arylalkyl groups include benzyl and phenylethyl.

"Heteroarylalkyl" is an alkyl moiety substituted with a heteroaryl group.

"Arylamino" is an amino moiety substituted with an aryl group (e.g., -NH-aryl).

"Aryloxy" is an oxygen atom having an aryl substituent (e.g., -O-aryl).

"Acyl" or "carbonyl" is a moiety formed by removal of the hydroxy from a carboxylic acid (e.g., R-C(=O)-). Preferred alkylacyl groups include, but are not limited to, acetyl, propionyl, and butanoyl.

"Acyloxy" is an oxygen atom having an acyl substituent (e.g., -O-acyl); for example, -O-C(=O)-alkyl.

"Acylamino" is an amino moiety having an acyl substituent (e.g., -N-acyl); for example, -NH-(C=O)-alkyl.

"Benzoxy": The benzoyloxy radical.

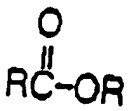
"Benzoyl": The aryl radical, C_6H_5CO-, derived from benzoic acid.

"Benzoyloxy": e.g., Benzoxy. The radical C_6H_5COO-, derived from benzoic acid.

"Carbamate": A salt of carbamic acid; it contains the $-NCO_2-$ radical, also known in the art as urethanes or carbamic esters.

"Carboxy": Prefix indicating the acidic carboxyl group.

"Ester": An organic salt formed from an alcohol (base) and an organic acid by elimination of water; functional group derivatives of carboxylic acids are those compounds that are transformed into carboxylic acids by simple hydrolysis. The most common such derivatives are esters, in which the hydroxy group is replaced by an alkoxy group.



"Glycoside": A natural compound of a sugar with another substance, which hydrolyzes a sugar plus a principle: (e.g., coniferin yields glucose plus coniferyl alcohol as the principle; glucosides yield glucose, fructosides yield fructose, galactosides yield galactose, etc.; the cyclic acetal of a carbohydrate.

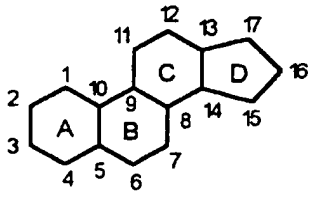
"Halo", "halogen", or "halide" is a chloro, bromo, fluoro, or iodo atom radical. Chloro, bromo, and fluoro are preferred halides.

"Lactone": Any of a class of inner esters of hydroxy carboxylic acids formed by the loss of a molecule of water from the hydroxy and carboxyl groups of the acids, characterized by the carboxyl-oxy grouping -OCO- in a ring, and classed according to the position of the hydroxy group in the parent acid.

A "pharmaceutically-acceptable" salt is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987, hereby incorporated by reference herein. Preferred cationic salts include the alkali-metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium). Suitable anionic salts include the halides (such as chloride) salts, as well as the carboxylate (such as maleate) salts. Preferred anionic salts include the maleate salt.

"Salts": Substances produced from the reaction between acids and bases; a compound of a metal (positive) and nonmetal (negative) radical: M . OH (base) + HX (acid) = MX (salt) + H_2O (water).

"Steroid nucleus": Generic name for a family of lipid compounds comprising the sterols, bile acids, cardiac glycosides, saponins, and sex hormones.



"Substituent": Any atom or group replacing the hydrogen of a parent compound.

"Substitute": To replace one element or radical in a compound by a substituent.

"Substituted": Pertaining to a compound which has undergone substitution.

"Substitution": A reaction in which an atom or group of atoms in a (usually organic) molecule is exchanged for another.

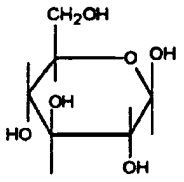
Substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include, but are not limited to, those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), hereby incorporated by reference herein. Preferred

substituents include, but are not limited to, alkyl, alkenyl, alkoxy, hydroxy, oxo, amino, aminoalkyl (e.g., aminomethyl, etc.), cyano, halo, carboxy, alkoxyacetyl (e.g. carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

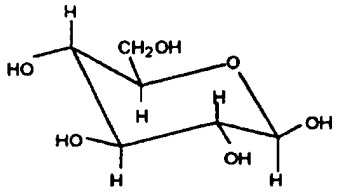
A "monosaccharide" is a single sugar moiety; e.g., hexose, 2-deoxyglucose, 6-deoxyhexose, 2,6-dideoxyhexose, etc., rhamnose, glucose, arabinose, digitoxose, fructose, galactose; rhamnopyranose, hexopyranose, 6-deoxyglucose, 4,6-dideoxy-glycopyranose, mannose, cymarose, xylose, lyxose, ribose, digitalose, 4-amino-2,4,6-trideoxylyxohexopyranose, 4-amino-4,6, dideoxyglucopyranose, 2,3-dideoxyrhamnopyranose, 4-methoxy 4,6-dideoxyrhamnopyranose.

An "oligosaccharide" is a sugar having 2-8 monosaccharide sugar residues, preferably 2-3. The last monosaccharide residue of the oligosaccharide is known as the "terminal" oligosaccharide residue.

The "monosaccharide" or "oligosaccharide" residue can be graphically depicted in either a ring or a chair configuration. For example, glucose (a monosaccharide) can be represented accordingly:



"ring"



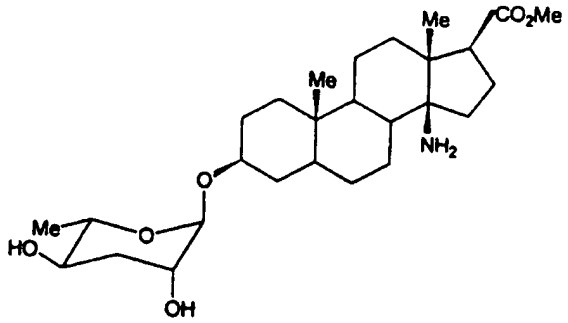
"chair"

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses certain deoxy or oxygen-substituted sugar-containing 14-aminosteroid compounds for use in the treatment of supraventricular arrhythmia and/or atrial fibrillation in humans or other mammals. Specific compounds and compositions to be used in the invention must, accordingly, be pharmaceutically-acceptable. As used herein, such a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or other mammals in the treatment of supraventricular arrhythmias and/or cardiac fibrillation and without undue adverse side effects (such as toxicity, irritation, and allergic response), commensurate with a reasonable benefit/risk ratio.

ACTIVE MATERIALS

Deoxy or oxygen-substituted sugar-containing 14-aminosteroid compounds and the pharmaceutically-acceptable acid salts or esters thereof of the general formula:

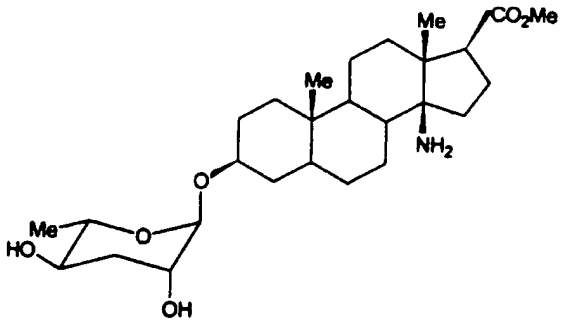


METHODS OF MANUFACTURE

The following non-limiting examples are illustrative of the methods of manufacture for the compounds of the present invention.

EXAMPLE 1

Synthesis of (3β, 5β, 14β, 17β)-14-Amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester

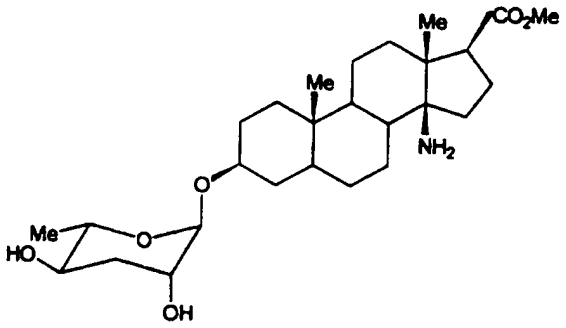


To a stirred solution of (3ß, 5ß, 14ß, 17ß)-14-Amino-3-[(3',6'-dideoxy-2',4'-O-dibenzoyl-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester (6.2 g, 9.2 mmol) in anhydrous MeOH (40 mL) at ambient temperature is added NaOMe (4.0 g, 73.6 mmol). The mixture is stirred for 24 h under N_2. Removal of the solvent under reduced pressure yields a white solid residue. This crude mixture is partitioned in $CHCl_3$ and H_2O. The aqueous layer is extracted with $CHCl_3$ three times. The combined extracts are washed with brine, are dried and are evaporated to yield a crude

product. Purification by chromatography (silica gel, eluded with CH_2Cl_2/MeOH/NH_4OH in gradient from 500 : 10 : 3 drops to 500 : 40 : 12 drops) provides a pure (3ß, 5ß, 14ß, 17ß)-14-amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester as white crystal.

EXAMPLE 2

Synthesis of (3β, 5β, 14β, 17β)-14-Amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester



(3β, 14β, 17β)-14-Amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester [prepared as described in Example 10 herein] can also be synthesized according to the procedure described below:

To a solution of (3β, 5β, 14β, 17β)-14-amino-3-[(3',6'-dideoxy-2', 4'-O-dibenzoyl-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester (200 g, 0.29 mol) [prepared as described in Example 26 herein] in a mixture of MeOH (2 L) and CH_2Cl_2 (1 L) is added NaOMe (16 g, 0.30 mol) with stirring at ambient temperature. The reaction mixture is allowed to stir for 24 hours and is then quenched by adding $NaHCO_3$ (54 g, 0.65 mol). This is stirred for 2 hours, filtered, and concentrated under reduced pressure to give an oily residue. The residue is then slurried in 10% heptane/methyl t-butyl ether (2.25 L) for 2 hours, filtered, and reslurried in water (1 L) for 2 hours. The product is obtained as a white solid upon filtration and drying.

ASSESSMENT OF PHARMACOLOGICAL ACTIVITY

Electrophysicological properties are assessed in whole animal models. The ability of the novel deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds of the present invention to favorably affect sinus node functional, heart rate, atrial effective refractory period, atrioventricular node effective refractory period,

sinus node recovery tiem and to terminate atrial fibillation/flutter refractory periods and atrial flutter are assessed.

PHARMACEUTICAL COMPOSITIONS

The deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds of the present invention may be administered to humans or other mammals by a variety of routes, including, but not limited to, oral dosage forms and injections (intravenous, intramuscular, intraperitoneal and subcutaneous). Numerous other dosage forms containing the deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds of the present invention can be readily formulated by one skilled in the art, utilizing the suitable pharmaceutical excipients as defined below. For considerations of patient compliance and chronic therapy, oral dosage forms are generally most preferred. For acute use, intravenous dose forms are preferred to rapidly terminate the arrhythmia.

The term "pharmaceutical composition" as used herein means a combination comprised of a safe and effective amount of the novel deoxy and oxygen-substituted sugar-containing 14-aminosteroid compound active ingredient, or mixtures thereof, and pharmaceutically acceptable excipients.

The phrase "safe and effective amount", as used herein, means an amount of a compound or composition large enough to significantly alleviate the symptoms and/or condition to be treated, but small enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of active ingredient for use in the pharmaceutical compositions to be used in the method of the invention herein will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient being employed, the particular pharmaceutically acceptable excipients utilized, and like factors within the knowledge and expertise of the attending physician.

The term "pharmaceutically acceptable excipients" as used herein includes any physiologically inert, pharmacologically inactive material known to one skilled in the art, which is compatible with the physical and chemical characteristics of the particular deoxy or oxygen-substituted sugar containing 14-aminosteroid compound active ingredient selected for use. Pharmaceutically acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, binders, lubricants, glidants, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives,

sweetening agents, flavoring agents, pharmaceutical grade dyes or pigments, and viscosity agents.

The term "oral dosage form" as used herein means any pharmaceutical composition intended to be systemically administered to an individual by delivering said composition to the gastrointestinal tract of an individual, via the mouth of said individual. For purposes of the present invention, the delivered form can be in the form of a tablet, coated or non-coated; solution; suspension; or a capsule, coated or non-coated.

The term "injection" as used herein means any pharmaceutical composition intended to be systemically administered to a human or other mammal, via delivery of a solution or emulsion containing the active ingredient, by puncturing the skin of said individual, in order to deliver said solution or emulsion to the circulatory system of the individual either by intravenous, intramuscular, intraperitoneal or subcutaneous injection.

The rate of systemic delivery can be satisfactorily controlled by one skilled in the art, by manipulating any one or more of the following:

(a) the active ingredient proper;

(b) the pharmaceutically-acceptable excipients; so long as the variants do not interfere in the activity of the particular active ingredient selected;

(c) the type of the excipient, and the concomitant desirable thickness and permeability (swelling properties) of said excipients;

(d) the time-dependent conditions of the excipient itself and/or within the excipients;

(e) the particle size of the granulated active ingredient; and

(f) the pH-dependent conditions of the excipients.

As stated hereinabove, pharmaceutically-acceptable excipients include, but are not limited to, resins, fillers, binders, lubricants, solvents, glidants, disintegrants co-solvents, surfactants, preservatives, sweetener agents, flavoring agents, buffer systems, pharmaceutical-grade dyes or pigments, and viscosity agents.

The preferred solvent is water.

Flavoring agents among those useful herein include those described in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, 1990, pp. 1288-1300, incorporated by reference herein. The pharmaceutical compositions suitable for use herein generally contain from 0-2% flavoring agents.

Dyes or pigments among those useful herein include those described in Handbook of Pharmaceutical Excipients, pp. 81-90, 1986 by the American Pharmaceutical Association & the Pharmaceutical Society of Great Britain.

incorporated by reference herein. The pharmaceutical compositions herein generally contain from 0-2% dyes or pigments.

Preferred co-solvents include, but are not limited to, ethanol, glycerin, propylene glycol, polyethylene glycols. The pharmaceutical compositions of the present invention include from 0-50% co-solvents.

Preferred buffer systems include, but are not limited to, acetic, boric, carbonic, phosphoric, succinic, malaic, tartaric, citric, acetic, benzoic, lactic, glyceric, gluconic, glutaric and glutamic acids and their sodium, potassium and ammonium salts. Particularly preferred are phosphoric, tartaric, citric, and acetic acids and salts. The pharmaceutical composition of the present invention generally contain from 0-5% buffer systems.

Preferred surfactants include, but are not limited to, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters and lanolin esters and ethers, alkyl sulfate salts, sodium, potassium, and ammonium salts of fatty acids. The pharmaceutical compositions of the present invention include 0-2% surfactants.

Preferred preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, o-phenylphenol benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chlorobutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetylpyridinium chloride, methyl paraben and propyl paraben. The compositions of the present invention generally include from 0-2% preservatives.

Preferred sweeteners include, but are not limited to, sucrose, glucose, saccharin, sorbitol, mannitol, and aspartame. Particularly preferred are sucrose and saccharin. Pharmaceutical compositions of the present invention include 0-5% sweeteners.

Preferred viscosity agents include, but are not limited to, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropyl-cellulose, sodium alginate, carbomer, povidone, acacia, guar gum, xanthan gum and tragacanth. Particularly preferred are methylcellulose, carbomer, xanthan gum, guar gum, povidone, sodium carboxymethylcellulose, and magnesium aluminum silicate. Compositions of the present invention include 0-5% viscosity agents.

Preferred fillers include, but are not limited to, lactose, mannitol, sorbitol, tribasic calcium phosphate, dibasic calcium phosphate, compressible sugar, starch, calcium sulfate, dextro and microcrystalline cellulose. The compositions of the present invention contain from 0-75% fillers.

Preferred lubricants include, but are not limited to, magnesium stearate, stearic acid, and talc. The pharmaceutical compositions of the present invention include 0.5-2% lubricants.

Preferred glidants include, but are not limited to, talc and colloidal silicon dioxide. The compositions of the present invention include from 1-5% glidants.

Preferred disintegrants include, but are not limited to, starch, sodium starch glycolate, crospovidone, croscarmelose sodium, and microcrystalline cellulose. The pharmaceutical compositions of the present invention include from 4-15% disintegrants.

Preferred binders include, but are not limited to, acacia, tragacanth, hydroxypropylcellulose, pregelatinized starch, gelatin, povidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, sugar solutions, such as sucrose and sorbitol, and ethylcellulose. The compositions of the present invention include 1-10% binders.

Compounds of the present invention may comprise from 0.1% to 99.9% by weight of the pharmaceutical compositions of the present invention. Preferably the compounds of the present invention comprise from about 20% to about 80% by weight of the pharmaceutical compositions of the present invention.

Accordingly, the pharmaceutical compositions of the present invention include from 15-95% of a deoxy and oxygen-substituted sugar-containing 14-aminosteroid compound active ingredient, or mixture, thereof; 0-2% flavoring agents; 0-50% co-solvents; 0-5% buffer system; 0-2% surfactants; 0-2% preservatives; 0-5% sweeteners; 0-5% viscosity agents; 0-75% fillers; 0.5-2% lubricants; 1-5% glidants; 4-15% disintegrants; and 1-10% binders.

Suitable pharmaceutical compositions are described herein. It is well within the capabilities of one skilled in the art to vary the non-limiting examples described herein to achieve a broad range of pharmaceutical compositions.

The choice of a pharmaceutically acceptable excipient to be used in conjunction with the deoxy or oxygen-substituted sugar-containing 14-aminosteroid compounds of the present invention is basically determined by the way the compound is to be administered. If the compound is to be injected, the preferred pharmaceutical carrier is sterile physiological saline, the pH of which has been adjusted to about 7.4. Suitable pharmaceutically-acceptable carriers for topical application include those suited for use in creams, gels, tapes and the like.

The preferred mode of administering the deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds of the present invention is oral. The preferred unit dosage form is therefore tablets, capsules and the like, comprising a safe and

effective amount of the deoxy or oxygen-substituted sugar-containing 14-aminosteroid compounds of the present invention. Pharmaceutically acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well known in the art. Their selection will depend on secondary considerations such as taste, cost, and shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral dosage forms comprise a safe and effective amount, preferably from 0.1 mg to 5.0 mg of the deoxy and oxygen-substituted sugar-containing 14-aminosteroid. More preferably these oral dosage forms comprise 0.25 - 1.0 mg of the deoxy and oxygen-substituted sugar-containing 14-aminosteroid. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents. Preferred carriers for oral administration include gelatin, propylene glycol, cottonseed oil and sesame oil.

The compositions of this invention can also be administered topically to a subject, i.e., by the direct laying on or spreading of the composition on the epidermal or epithelial tissue of the subject. Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions comprise a safe and effective amount, preferably from 0.5 mg to 2.0 mg, of the deoxy and oxygen-substituted sugar-containing 14-aminosteroid. More preferably these topical compositions comprise 1.0 mg of the deoxy and oxygen-substituted sugars-containing 14-aminosteroid. Suitable carriers for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the deoxy and oxygen-substituted sugar-containing 14-aminosteroid. The carrier may include pharmaceutically-acceptable emollients, emulsifiers, thickening agents, and solvents.

The compositions of this invention can also be administered via the inhalation route. Such compositions are prepared in a matrix comprising a solvent such as water

or a glycol, preservatives such as methyl or propyl paraben and propellants such as nitrogen or carbon dioxide.

Additionally, the compositions of this invention can be administered via a subcutaneous implant formed from silicone elastomers, ethylene vinyl acetate co-polymers or lactic-glycolic co-polymers.

In order to illustrate how to prepare pharmaceutical compositions containing the novel compounds of the present invention, the following non-limiting pharmaceutical composition examples are presented.

PHARMACEUTICAL COMPOSITION EXAMPLES

EXAMPLE 1

An immediate release oral dosage form (tablet) containing the (3ß,5ß,14ß,17ß)-14-Amino-3-[3',6'-dideoxy-α-L-mannopyranosyl)oxy]androstane-17-carboxylic acid, methyl ester has the following composition:

Active Ingredient	Amount
(3ß,5ß,14ß,17ß)-14-Amino-3-[(3',6'-dioxy-α-L-mannopyranosyl) oxy]androstane-17-carboxylic acid, methyl ester	1.0 mg
Excipients	
Microcrystalline cellulose	28.5 mg
Lactose, hydrous	67.2 mg
Crospovidone	3.0 mg
Magnesium stearate	0.3 mg

Manufacturing directions: (for 10,000 tablets)

1) 10.0 g of the drug, 285.0 g of microcrystalline cellulose, 672.0 g of lactose and 30.0 g of crospovidone are mixed in a Patterson-Kelley (PK) or other suitable blender,
2) the above mixture is blended with 3.0 g of magnesium stearate in a PK or suitable blender,
3) the above final blend is compacted into 100.0 mg tablets on a suitable tableting machine.

EXAMPLE 2

A parenteral dosage form containing the (3ß,5ß,14ß,17ß)-14-Amino-3-[(3',6'-dioxy-α-L-mannopyranosyl) hydrochloride and suitable for use as an intravenous (I.V.) injection has the following composition:

Active Ingredient	Amount
(3ß,5ß,14ß,17ß)-14-Amino-3-[(3',6'-dioxy-α-L-mannopyranosyl) oxy]androstane-17-carboxylic acid, methyl ester	1.0 mg
Excipients	
Mannitol	200.0 mg
Citric acid/sodium citrate	quantity sufficient to adjust the pH between 5.5 - 6.5

Manufacturing directions: (for 1000 vials)

1) 1.0 g of the drug, 200.0 g of mannitol and sufficient sodium citrate and citric acid are dissolved in 2200.0 ml of sterile, deionized water for injection,
2) the above solution is filtered through a 0.22 micron sterile membrane filter,
3) 2.2 ml of the above sterile solution is filled into Type I glass vials and then lyophilized in a suitable lyophilizer,
4) the vials, after lyophilization, are stoppered with bromobutyl or other suitable stoppers and sealed. The lyophilized product is reconstituted with 2.0 ml of sterile water for injection immediately prior to use.

EXAMPLE 3

A sustained release oral dosage form (tablet) containing the (3ß,5ß,14ß,17ß)-14-Amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)oxy]androstane-17-carboxylic acid, methyl ester has the following composition:

Active Ingredient	Amount
(3ß,5ß,14ß,17ß)-14-Amino -3-[(3',6'-dideoxy-α-L-mannopyranosyl)oxy]androstane-17-carboxylic acid, methyl ester	5.0 mg
Excipients	
Hydroxypropylmethylcellulose	120.0 mg
Lactose, hydrous	120.0 mg
Magnesium stearate	12.0 mg
Colloidal silicon dioxide	4.0 mg

Manufacturing directions: (for 10,000 tablets)

1) 50.0 gm of the drug, 1.2 kg of hydroxypropylmethylcellulose and 1.2 kg of lactose are mixed intimately in a twin shell Patterson-Kelley or suitable mixer,
2) to the above mix are added 120 gm of magnesium stearate and 40 gm of colloidal silicon dioxide and this is lightly blended in a suitable mixer,
3) the above blend is compacted into tablets weighing 261.0 mg on a suitable tablet press.

MISCELLANEOUS EXAMPLES

In addition to the above three examples, the drug active ingredient is formulated into a number of different dosage forms:

1) a pharmaceutical aerosol containing solvent (e.g. water, glycols), preservatives (methyl or propyl parabens) and propellants (nitrogen, carbon dioxide) or other suitable excipients,

2) a rectal suppository containing theobroma oil or polyethylene glycols,

3) a subcutaneous implant containing silicone elastomers, ethylene-vinyl acetate copolymers, lactic-glycolic copolymers and hydrogels or other suitable polymers,

4) commercially available implantable devices,

5) a transdermal system containing silicone fluid in an ethylene-vinyl acetate copolymer membrane or other suitable ingredients for delivery with or without the aid of iontophoresis,

6) a buccal mucoadhesive patch containing hydrocolloid polymers (hydroxyethyl cellulose, hydroxy-propyl cellulose, povidone) and other suitable polymers.

METHODS OF TREATMENT

The novel compounds of the present invention are efficacious in treating humans or other mammals afflicted with supraventricular arrhythmias and/or atrial fibrillation. As stated hereinabove, except in rare cases, supraventricular arrhythmias are not deemed to be life threatening and are generally not aggressively treated with conventional antiarrhythmic drugs due to their undesirable side effects. Accordingly, this type of arrhythmia is usually not aggressively treated to merely relieve symptoms which are characterized as mild to severe. However, if untreated this type of arrhthmia may lead to strokes of if chronic may cause CHF. The compounds of the present invention are generally well tolerated and exhibit a different electrophysiological effects than do many of the more conventional cardiac glycosidic drugs, and may be an acceptable therapy to alleviate the symptoms suffered by individuals exhibiting supraventricular arrhythmias who are experiencing discomfort, even though not in an immediately life threatening situation.

The present invention relates to a method for treating a human or other mammal suffering from supraventricular arrhythmia and/or atroa; fibrillation which comprises administering to said human or other mammal a safe and effective amount of a pharmaceutical composition comprising by weight of the composition from 15-90% of a substituted sugar-containing 14-aminosteroid compound, and from 10-85% pharmaceutically acceptable excipients.

In order to illustrate the particular utility of these unique deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds, for the treatment of arrhythmia. the following non-limiting clinical examples are presented.

CLINICAL EXAMPLES

EXAMPLE 1

Patient X has a "tachy-brady" syndrome. Digoxin controls his tachycardia but produces such low heart rates that he is somewhat symptomatic. His bradycardic episodes are not frequent. He is switched to (3β, 5β, 14β, 17β)-14-Amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester. The tachycardias are controlled without severe bradycardia.

EXAMPLE 2

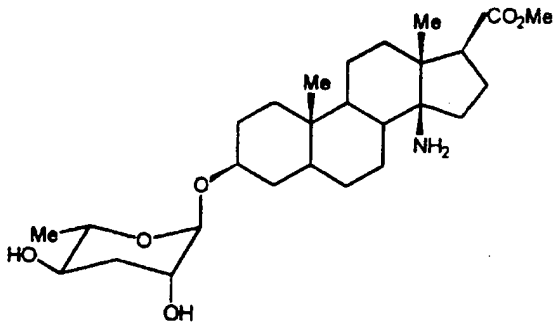
Patient Y is on digoxin and has atrial fibrillation with a ventricular rate of 85. However, he has very little cardiac reserve. His physician would prefer him in sinus rhythm to increase his cardiac output. He is switched from digoxin to (3β, 5β, 14β, 17β)-14-Amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester. He converts to sinus rhythm and with the increased cardiac output due to the added contribution of the atrial contraction to ventricular filling. The patient is doing much better.

EXAMPLE 3

Patient Z is on digoxin and has atrial fibrillation with a ventricular rate of 85. He has low cardiac reserve, so needs inotropic support. However, his physician is concerned about his patient having a stroke due to the arrhythmia. The patient has a history of frequent falls so the physician does not want to anticoaqulate the patient. The patient is switched from digoxin to (3β, 5β, 14β, 17β)-14-Amino-3-[(3',6'-dideoxy-α-L-mannopyranosyl)-oxy]-androstane-17-carboxylic acid methyl ester. He converts to sinus rhythm and does well. His cardiac output is increased due to the added contribution of the atrial contraction to ventricular filling.

WHAT IS CLAIMED IS:

1. The use of a safe and effective amount of a deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds and the pharmaceutically-acceptable acid salts or esters thereof of the formula:



in the manufacture of a medicament for treating chronic or acute supraventricular arrhythmia or atrial fibrillation.

2. The use according to Claim 1 wherein said deoxy and oxygen-substituted sugar-containing 14-aminosteroid compounds and the pharmaceutically-acceptable acid salts or esters in the medicament comprise, by weight of said composition, from 15 to 95% of said compound and from 5 to 85% pharmaceutically-acceptable excipients.

3. The use according to Claim 2, wherein the pharmaceutically-acceptable excipients are selected from the group consisting of polymers, resins, plasticizers, fillers, binders, lubricants, glidants, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes or pigments, and viscosity agents.

4. The use according to Claim 3 wherein said pharmaceutical composition comprises of from 15-95% of a compound of Claim 1 (or mixtures thereof); 0-2% flavoring agents; 0-50% co-solvents; 0-5% buffer system; 0-2% surfactants; 0-2% preservatives; 0-5% sweeteners; 0-5% viscosity agents; 0-75% fillers; 0.5-2% lubricants; 1-5% glidants; 4-15% disintegrants; and 1-10% binders.

5. The use according to Claim 4 wherein said pharmaceutical composition is in an oral dosage form.

6. The use according to Claim 3 wherein said pharmaceutical composition is an intravenous dosage form.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 97/10453

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 08558 A (PROCTER & GAMBLE) 30 March 1995 cited in the application * p.23, 1st compound; Ex. 3; p.70, l.19-20 * ---	1-6
Y	WO 95 01335 A (MERCK & CO INC ;BALDWIN JOHN J (US); CLAREMON DAVID A (US); ELLIOT) 12 January 1995 * p.1, l.5-8; p.4,l.29-30; p.11, l.5-8 * ---	1-6
Y	CUMMINGS ET AL: "Positive inotropic and antiarrhytmic actions of actodigin in dogs" ARCH. INT. PHARMACODYN., vol. 228, 1977, pages 92-8, XP002042448 * abstract; p.97-98, Discussion * --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1997	27. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uiber, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr. .nat Application No
PCT/US 97/10453

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 885 280 A (JARREAU FRANCOIS-XAVIER ET AL) 5 December 1989 cited in the application * col.1, l.45-col.2, l.2 *	1-6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/US 97/10453

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9508558 A	30-03-95	AU 7800994 A	10-04-95
		BR 9407613 A	14-01-97
		CA 2172497 A	30-03-95
		CN 1135757 A	13-11-96
		CZ 9600867 A	16-10-96
		EP 0720616 A	10-07-96
		HU 74610 A	28-01-97
		JP 9502983 T	25-03-97
		NO 961169 A	24-05-96
		PL 313621 A	08-07-96
WO 9501335 A	12-01-95	US 5382587 A	17-01-95
		AU 7253994 A	24-01-95
US 4885280 A	05-12-89	FR 2621316 A	07-04-89
		AU 2293588 A	06-04-89
		CA 1306248 A	11-08-92
		DE 3873870 A	24-09-92
		EG 19114 A	30-07-94
		EP 0310519 A	05-04-89
		ES 2052761 T	16-07-94
		HK 60297 A	16-05-97
		IE 61941 B	30-11-94
		IL 87894 A	27-02-94
		JP 1156995 A	20-06-89
		KR 9702642 B	07-03-97